DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

PLENARY SESSION

Wednesday, February 16, 2005

8:30 a.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
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C O N T E N T S

P R O C E E D I N G S

Opening Remarks

DR. CHEN: Welcome back to the FDA/DIA Workshop on Follow-on Proteins from Pharmaceuticals. This will be the third and last day of the program and, as Co-Chair of the Planning Committee, I would like to thank you for your participation so far. My name is Chi-Wan Chen. I am Deputy Director for the Office of New Drug Chemistry in the Office of Pharmaceutical Science in CDER.

We will have a half-day program today starting with reports from three breakout sessions, D., E. and F. followed by a break. Then there will be a summary of the workshop from different perspectives represented by the innovators, the generic industry FDA. Then we will wrap up the workshop with closing remarks from FDA.

So I hope you stay with us. Thank you for coming back this morning. I know some people may have already returned home.

The first part of this morning's program

is the reports from three sessions. Actually, I think I need to take this opportunity to make a quick announcement on two logistics which you may be interested in knowing. First, the slides for the presentations over the last two days will be available on the DIA website. However, they are password-protected so each attendee here will receive a personalized e-mail from DIA, probably Friday, no later than Friday, with the instruction on how to access the website.

Secondly, all the sessions, including the plenary sessions, have transcripts. They are transcribed. If you would like to access that, you can expect an e-mail, individualized again, from DIA within about 30 days with instructions how to get it. The plan right now is that you will have to request such a transcript. Because of the size of it, it will probably be on a CD-ROM. But it will only be sent out upon request.

For the breakout session reports, the first one will be presented by Dr. Dena Hixon on clinical pharmaceutical studies. Dr. Hixon is

Associate Director for Medical Affairs in the Office of Generic Drugs in CDER.

Dr. Hixon.

Clinical Pharmacology Studies

DR. Hixon: Thank you. Good morning. Before I start with the summary of this breakout session, I think there is one point of clarification I would like to make. As I have been reflecting on some of the comments we heard in the breakout session and also some of the comments that were made during the plenary session yesterday, it occurred to me that we may not all be on exactly the same page with regard to the range of products that we are considering.

The title of the workshop includes the term "follow-on protein pharmaceuticals." I realize from some of the comments that had been submitted to the docket that some of, especially, the innovator companies who are involved, have limited their consideration to follow-on biologicals which are at the more complex end of the range.

I just want to bring this up because there certainly are protein products that range all the way down to the peptide products. There is no real

clear cut-off in FDA in terms of what is considered a peptide and what is considered a protein and there also are some not very-well-defined boundaries between some of the simpler protein products and some of the more complex products.

The fact that we are taking a very close look at the approach to follow-on biologicals and follow-on protein products in general brings a fair amount of scrutiny to any follow-on products for the simpler proteins as well. I think that, therefore, some people in the audience may be including the simpler products in their considerations as well as these more complex products.

I specifically wanted to add that I had some discussion with Dr. Velagapudi yesterday because he had mentioned, in his presentation to the Plenary Session, the concept of waivers of in vivo bioequivalence requirement and the concept of

avoiding unnecessary clinical trials.

Dr. Velagapudi clarified for me what is focus was in discussing the use of PK and PD parameters for the entire spectrum of protein products and, perhaps, drug products in general. Of course, there are some very simple, very well characterized peptide products that have, in fact, been approved as generics with a waiver of the in vivo bioequivalence study requirement.

Dr. Velagapudi clarified that is the kind of product that he was talking about. He certainly did make the comment that use of waivers would be very infrequent. So I want to put some people at ease that that discussion wasn't intended to say that waivers would be a consideration for the very complex protein products.

Having said that, I will go through my summary with the realization that some of the summary may not actually apply to the very simple products because most of the people present at the breakout session were really concentrating on the more complex products.

Our breakout session on clinical pharmacology was asked to answer three questions; what information does a PK study provide; what

additional information of value would a PD study provide; and what factors affect study design and establishment of acceptable limits for PK/PD comparison.

I think the group actually had a little bit more agreement than they realized they did and, when we summarized at the end of each breakout session, it was clear that the entire group recommended that PK studies are a necessary part of the evaluation of comparability but may not always be enough.

There also was discussion about the usual bioequivalence limits which are a 90 percent confidence interval between 0.80 and 1.25. The group, as a whole, believed that this interval limit may be too tight for protein products but also agreed that, if a product falls within those limits with regard to PK, that this may reduce the uncertainty of the PK comparability.

There also was agreement that pharmacodynamics may be a useful adjunct to reduce uncertainty especially when there is a validated endpoint. Although I didn't include this in my slides, it was also pointed out that PK and PD studies would best be performed together when that

is possible rather than doing a PK study and then realizing maybe PD would be useful and having to do an additional study because they often can be done at the same time.

There also was consensus that there is a role for clinical data in some cases and that a case-by-case evaluation is needed depending on prior experience with the product.

Information that can be gained from a PK study include evaluation of systemic exposure in terms of blood concentrations, evaluation of formulation comparability and note was made that plasma PK does not reflect biodistribution. You can have equivalent plasma PK but, in some cases, might have different delivery to different tissues in the body and also plasma PK does not always

reflect similar efficacy and safety between products.

There were some recommendations with regard to PK study design. It was noted that, although crossover studies are generally recommended for evaluation of bioequivalence, that they should be used with caution for protein products as immunogenicity may affect the results. A parallel design may be more useful in some situations, particularly situations where immunogenicity is an issue and where there is a particularly long half-life. Again, the design of PK studies should be developed on a case-by-case basis.

Again, it also was recommended that comparative studies should use a clinically relevant dose that is most likely to show a difference between products.

Information that may be gained from pharmacodynamic studies; these studies may be useful as an adjunct to pharmacokinetics. Validated endpoints are generally needed.

Appropriate endpoints for one indication may not always--maybe never--be extrapolated to a different indication and the 90 percent confidence interval of 80 to 125 percent may be too stringent for pharmacodynamic endpoints. It was noted that PD variability of the reference product may actually facilitate interpretation of the comparability in PD studies.

Additional points of discussion related to the need for clinical data beyond PK comparability; it was felt that the need for clinical data depends on the following factors: complexity of the molecule. Obviously, the more complex the molecule, the more need there is for PK but also it may be less reliable; availability of assays that have the ability to establish physicochemical identity and the reliability or level of confidence that one can have in those results also plays into the need for and the interpretation of PK studies.

Also, the therapeutic context of the product; the availability of validated PD markers; the variability in PD markers and the clinical

implications of immunogenicity.

It was noted that the amount of uncertainty about comparability from the analytic studies is relevant to the utility of PK. Also, animal PK study results may be useful in designing human comparability studies but animal PK or PD sameness may not be relevant to humans.

It was pointed out that if animal PK and PD studies are done and show wide differences between products, that that may actually be a reason to abandon a product whereas showing sameness for PK or PD in animal studies may simply be a reason to proceed with development and proceed with the other necessary studies.

One cannot extrapolate clinical performance in one clinical situation with another clinical use that has a different mechanism of action. At least as much information is needed for a follow-on product as for a change from the investigational to the to-be-marketed formulation of the same manufacturer.

There were several points where the group

did not reach agreement. This was mostly regarding whether PK can be adequate for demonstrating comparability in some cases. Some suggested that PK should be enough in the setting of physicochemical sameness and others suggested the further clinical studies are always needed.

There was some discussion about the fact that most of the available examples of significant PK differences involved products with discernable physicochemical differences. One could argue that, if there are discernable physicochemical differences, that that takes the product out of consideration for a follow-on product and that, therefore, this may not be relevant.

However, it was also pointed out that the lack of approved follow-on products at this point means there really is not a lot of information available with regard to PK similarity or differences in products that do appear to be as similar a possible from a physicochemical standpoint

This is basically the end of our summary

of the session. I would welcome any comments or disagreements that anybody from the group had. I also want to thank everybody for their participation. It was a good session and I think we had some very useful discussion.

Are there any comments or questions? I will turn it back to you.

DR. CHEN: Next, Dr. Amy Rosenberg will report on immunogenicity studies. This is probably one of the liveliest discussions of all. Dr. Rosenberg is Director of the Division of Therapeutic Proteins in the Office of Biotechnology Products in OPS/CDER.

Dr. Rosenberg

Immunogenicity Studies

DR. ROSENBERG: Good morning, all. In spite of the post-prandial slump, I would say, we did manage to have some lively sessions and I thought that they were very good sessions in that they were to the point. People stayed on target and I think we actually did make some progress.

So we had four questions. Actually, one

of the questions was subsumed, in good part, within another question so I would say we had three principal questions. They focused on immunogenicity as it relates to product-quality attributes, to animal testing and to clinical testing.

So the first question focused around whether immunogenicity could be predicted from product-quality attributes. So the question is, and immunogenicity of protein products be predicted by biochemical or analytical techniques alone. We considered many of the factors which have been strongly related to immunogenicity including three-dimensional structure, all manor of impurities, leachables, excipients and product degradants, particularly aggregates and oxidized and deaminated species.

I think there was good consensus that, for such assessments, that sensitive, rigorous and current methods should be used to analyze the similarity between follow-ons and innovators. But the conclusion was that biochemical parameters,

although an important part of the characterization of proteins are not sufficient, of themselves, to predict immunogenicity of proteins so that, in fact, other studies are essential.

So then we moved into in vivo studies and started with the reasonable question as to whether there are any animal models which were useful in predicting immunogenicity; that is, in comparing innovator to follow-on proteins. This is a little bit of a different situation from asking whether an animal model can predict immunogenicity. That is not what we were asking. We were asking whether an animal model in which you would expect immunogenicity could pick up differences between two protein products.

So it was felt that animal studies can, indeed, be useful in demonstrating differences between innovator and follow-on products although you really need to have a window. You really need to see differences in a few key attributes of immunity so the studies in animals could examine and, perhaps, show differences or similarity in

terms of the titer, the maximum titer, achieved, whether there is cross-reactivity, neutralization, whether the antibodies actually neutralize product activity or not.

The kinetics of development and duration of the response are key because you can imagine that human proteins in lower animals are immunogenic because animals make responses to xeno components and, if that is a very strong response, then you might not have a window for seeing a difference. In addition, antibody isotype should be assessed.

However, it was conceded that the absence of a clear signal--that is, of a clear difference in immune-response parameters--doesn't equate with the absence of a problem. It is also thought that any positive signal, any clear difference, might indicate a significant difference between two products.

It was further agreed that no animal study could truly substitute for human trials but that a good animal study can reduce the extent of a human

immunogenicity study, perhaps, as well as influence the extent of data collected pre- versus post-approval; that is, in the scenario where the animals make a similar response to different protein products.

As I said before, a clear difference would signal something in the reverse direction, that there may be distinct differences that would require, perhaps, a larger or more extensive study.

We discussed the utility of the transgenic animal models, the human protein transgenic models. While this was felt to be a very promising sort of endeavor and something that might really be helpful in discriminating immunogenicity, that, at this point, it is largely experimental and very costly, indeed, to do.

So, lastly, we considered what trial designs would be most helpful in determining whether the follow-on is comparable to the innovator with respect to immunogenicity, and that is what clinical trial designs. It was certainly agreed on that one could not compare assays across

different products because assays have their own characteristics, their own sensitivities. So you cannot directly compare one group's assay and results from that assay to another.

So, given differences in the key attributes of antibody assays, and in the inability to compare immunogenicity data across products, side-by-side comparisons may well be advantageous and certainly advisable.

However, if such a comparative study is not to be done, then a single-arm immunogenicity study of the follow-on may be adequate if it is capable of assessing the extent of the immune response and of the impact of that immune response on safety and efficacy.

So, in further considerations to guide trial design, we thought that a risk assessment was essential so that the risk posed by the immune response to the product should be a factor in clinical-trial design to assess immunogenicity. Indeed, this risk should affect the size of the trial and/or the amount of data to be collected

pre- versus post-marketing.

Moreover, the history of the innovator product with respect to immunogenicity should be considered in the clinical-trial design and in the timing of collection of data.

So, I thought there was certainly more consensus than I was hoping for. So I was very pleased with the outcome, pleased to come to these conclusions. Obviously, there are a lot of details embedded in these conclusions that will need to be worked out but I think we are off to a very good start.

So I would like to thank my co-moderators as well as all who participated. So thank you. Does anybody have any questions? That clear? Okay. Thank you.

DR. CHEN: Sounds like there is more consensus than disagreement. That is encouraging. In fact, we have seen and heard a lot of very healthy, constructive scientific debate over the last two days and we are happy to see that consensus has emerged on certain issues.

Next, I would like to introduce Dr. David Orloff who will report on the breakout session in clinical safety and efficacy studies. Dr. Orloff

is Division Director for the Division of Metabolic and Endocrine Drug Products in CDER.

Clinical Safety and Efficacy Studies

DR. ORLOFF: Good morning. It is either consensus or people are burned out from fighting. You decide.

What I am going to do is give you a brief overview of some of the approaches, or really the general approaches, that were proposed in the plenary and then, for all intents and purposes, I think, reiterated by the two speakers at the breakout sessions.

From that point, I will move into a summary of some of the items that came up in the discussion of the specific questions that were posed to us and are included in your agenda. Then I will summarize the summary.

So, with regard to approaches to the program as posed in the plenary, at which, I

imagine, most of you were present, one of the speakers took the position that non-clinical testing--that is to say, all of the studies that are done up to the point of clinical trials of safety and efficacy--those studies are never all informative. There are always unknowns that remain at the end of those.

But the question we have to ask is how do we decide when and what clinical studies are--and he didn't say it, but I say it, in brackets--absolutely needed because, as an aside, another point that was raised by a number of speakers was, really, this question of--I guess, I would phrase it as more is always better but what is absolutely needed to establish safety and efficacy of a follow-on.

So, in order to decide when and what clinical studies are absolutely needed, there is a "depends" here. It depends on the level of concern that exists of significant inferiority with regard to safety and/or efficacy after the non-clinical product workup. That would be the chemical

characterization and the PK/PD, for example.

That breaks down into two fundamental questions; how likely, or unlikely, is the possibility of inferior safety or efficacy and how inferior might it actually be. What is the worst-case scenario. So, for example, is there a reasonably likelihood of a safety concern that could actually result in serious morbidity or morality for patients that doesn't exist or that is mitigated, at least based upon the--or is less prominent for the innovator.

Is the worst-case scenario an immunogenicity problem? Of course, we didn't address that specifically but, obviously, the severity of immunogenicity or the clinical significance of various immunogenicity responses is quite wide. Is there a true toxicity that might be novel that needs to be excluded? And another example given was with regard to inferior efficacy in a serious condition; that is to say, if the target condition is one that is serious and life-threatening or, perhaps, one where the patient

really only gets one crack, one bite at the apple, with regard to treatment, the possibility of inferior efficacy might be something that requires more attention.

Another approach, now wholly different but raises some other issues that played into our discussion, begins with the following point, that the quantity of evidence--and this is the concept of the spectrum of complexity of follow-on patient products--the quantity of evidence needed to conclude clinical comparability varies across the complexity spectrum of protein products. In other words, some hold that, as a matter or course, simple products ought to be--we ought to be able to bring them forward with less--I am not saying less rigor, but the overall complexity of the development program could be reduced as compared to highly complex products.

Specifically, clinical safety and efficacy studies, excluding, perhaps, the issues of potential immunogenicity, are not needed for low-complexity products. I will say more a little

bit later about where we didn't get to in definitions.

When clinical studies are merited, they should be, or they may well be, targeted clinical studies that address residual uncertainties after the nonclinical workup or some experience that is in the public domain with the innovator product or the class of products of which the follow-on is a part, or is a member. Postmarketing surveillance is there for all product follow-ons as it is for innovator biologics and protein products as it is for small-molecule drugs.

So here were the questions that we were posed. Numbers 1 and 2 sort of meld one into the next and it was, frankly, difficult for us in the discussion to distinguish them and, therefore, difficult for me in my summary to do so, but I have tried.

The first question is, in which situations would clinical safety and efficacy studies be needed and why. Number 2 is what factors should be considered in designing appropriate and relevant

clinical studies. Number 3, what concerns can be addressed by a postmarketing surveillance as a part of risk management.

So, Question No. 1; when are clinical studies needed. One of positions that was voiced multiple times by several individuals was that "experience--" and I put it in quotes because experience is not, per se, defined--I have added perhaps related to problems of variable safety and efficacy and immunogenicity across the manufacturing and marketing history of a product--informs judgment concerning the need for clinical studies so that there is an institutional memory that allows a conclusion--I kind of call this, jokingly, and I don't mean to--

[Interruption; fire alarm.]

DR. ORLOFF: All right. Hold that thought.

[Interruption; building evacuation.]

DR. CHEN: Welcome back. A second welcome back. I was wondering what to do with the extra time we had until this happened. So I am glad most

of you did come back, if not all of you. Dr. Orloff will resume his presentation. In addition, another brief announcement. The summaries from the breakout sessions will be posted on the FDA website.

DR. ORLOFF: FDA and not DIA?

DR. CHEN: Both. But the DIA will be a different type of access, as I explained earlier.

DR. ORLOFF: Okay. Ground Hog Day. Start again. I hope whoever was smoking in bed this morning is truly embarrassed.

So, I have been asked to start again because it was so scintillating the first time. As I said before, I will give you a brief overview of some of the approaches that were proposed at the plenary and then reiterated, question discussions and then try to give you what I see as the summary.

So, one position is that, given that non-clinical testing is never all-informative--there are always unknowns at the end--how do we decide when and what clinical studies are absolutely needed. The "absolutely,"

as I said before, is about the fact that unnecessary studies are just that. What we are talking about is what is needed absolutely to establish safety and efficacy of a follow-on product.

In order to answer this question, you first have to take into account the level of concern of the existence of significant inferiority with regard to safety or efficacy after the non-clinical product workup, so up to and including chemical characterization and PK/PD.

Within that, the questions would be, how likely or unlikely is the possibility of inferior safety or efficacy and, as I said, what is the worst-case scenario; how inferior might it actually be. Might it be such that a morbid or mortal event might accrue, that serious or not-so-serious immunogenicity might be the result, not the topic of our breakout session, per se, that there is a novel, true toxicity that might emerge or that, in the case of considerations of inferior efficacy, you might lose a window of opportunity in a serious

condition or, as I said, where there is one bite at the apple for a patient.

The secondary series of considerations I have called Approach 2 begins with the concept of the spectrum of complexity of follow-on protein products and holds that the quantity of evidence needed in order to conclude clinical comparability with regard to safety and efficacy should vary across that spectrum.

Specifically, in the case of low-complexity products, clinical safety and efficacy studies excluding issues of potential immunogenicity that would have to be investigated in humans might not be needed. On the other hand, for high-complexity products or as you went to more highly complex products, the converse would be true, that there might be an absolute need for clinical safety and efficacy studies.

Whatever clinical studies are conducted should be targeted to specifically address the uncertainties that remain after the non-clinical workup; that is to say, there is no a priori reason

that the follow-on--well, I guess it is sort of a truism that, if we are talking about follow-ons, then, by definition, we are talking about some abbreviation of the workup.

So, assuming that there is allowance for follow-ons, then the full workup is not needed. Targeted clinical studies are going to be the solution or the approach. Postmarketing surveillance is there for all marketed products, follow-ons, innovators, small molecules, proteins.

Questions; in which situation would clinical safety and efficacy studies be needed and why. What factors should be considered in designing appropriate and relevant clinical studies and what concerns can be addressed by the postmarketing surveillance?

With regard to when are clinical studies needed, one position that was voiced was the so-called experience position or what I have called the experience position; that is to say, experience in manufacturing, marketing, dealing with changes in process and, I guess, unspoken, the problems

that have been observed of variable safety, efficacy or immunogenicity, informs the judgment concerning the need for clinical studies going forward so that an institutional memory in some people's minds is critical to actually understanding what is critical in manufacturing.

The elements of that experience, again, are the manufacturing processes, what are critical steps, critical parameters to follow. What is the history of product development and, obviously, the marketing history with regard to clinical experience.

I have added, in parentheses--this was not explicitly stated at our meeting but I feel the need--at our breakout session--I feel the need to express kind of the obverse, if you will, that if there is a certain experience in some cases that informs an understanding of what is critical, then there must also be some cases in which there is an experience that available more generally--for example, the history of manufacturing of multiple products, presumably the same products although not

deemed as such from a regulatory standpoint--using multiple processes and long-term marketing of these products without appreciable clinical safety or efficacy issues may be cases in which studies are not needed. And we can talk about that if people want to later.

So, when people were asked to really be more specific about when studies were needed, there was a--many people voiced the opinion that any major process change, and that major process change that was most frequently expressed or mentioned was a change in the cell line from the innovator, should dictate clinical studies.

The example for the innovator industry--one of the examples was given for epo products. That is to say, based upon the well-known product history in this area--that is, by the way, in the public domain--there is a heightened sensibility to any changes in manufacturing with regard to epo products. So the innovator manufacturers say that that meets a threshold for clinical studies.

Another example was given in which a change in pharmacokinetic profiles of an innovator product after a manufacturing change necessitated,

in their mind, de novo clinical investigations. So that led to the conclusion that if there was a difference in the pharmacokinetics from the innovator then, obviously, that would necessitate further definition of comparability with regard to clinical safety and efficacy in a clinical trial.

The question was raised by, not a dissenter but on the other side, but if rigorous pharmacokinetics and pharmacodynamic comparisons show similarity, you may not need efficacy and safety studies. It seems self-evident, perhaps.

One person raised the issue that, perhaps, a lower threshold for requiring safety and efficacy studies should be in existence for chronic-use products; that is to say, if you think about what the--and, I guess, by extension, one might also say that potentially for products that are going to go into wider populations, there might be a lower threshold.

If you look at the length and breadth of potential exposures to a follow-on product, it might raise another level of concern with regard to the potential for risk. And there was consensus that there was an inability to predict immunogenicity based upon non-clinical studies.

That is what Amy covered as well.

With regard to the appropriate and relevant clinical studies, some general concepts. This have seemed to follow through a lot of discussion. The chemical complexity and knowledge of the specificity and the mechanisms of action of the product are important to the level of the study required. I think I will say more about that in a little bit.

But there were no definitions at any time of what constitutes a well-characterized protein product and what--how you define complexity. That wasn't in our discussion.

As a general rule, with regard to what are the relevant clinical studies, this was sort of guidance without specifics, that studies to qualify

major process changes should, at a minimum, be those to quality follow-ons.

Again, with regard to what studies, several people stated that surrogates, biomarkers or intermediate pharmacodynamic measures were useful and often sufficient for efficacy I think with the caveat that the more you know about the pharmacology and the mechanism of action of the protein product, whether or not the so-called surrogate is validated as a predictor of clinical benefit if it is a true marker, documented marker, of drug effect, then it becomes useful.

To repeat, validation, per se, is not needed, as stated by some. For example, raising hemoglobin in chronic renal failure with erythropoietin is known to improve outcomes so you need not reprove that concept if you are bringing forward a novel erythropoietin product. You simply need to prove that it raises hemoglobin. Likewise, perhaps even in a more simplistic manner, since it is known already that lowering glucose is good for diabetics, you don't have to show--you don't have

to repeat the diabetes control and complications trial or the UKPDS, but you do have to show that your insulin product has glucose-lowering activity.

In some instances, you may need to bridge--again, depending on knowledge of mechanisms of action and the potential or the existence of shared mechanisms across different clinical effects of drugs, you may need to bridge multiple separate indications with separate studies.

Our postmarketing discussion was really pretty broad-ranging. I think, like a lot of our discussion, it raised more questions than it actually answered. One of the questions that we didn't have an answer to was should postmarketing surveillance replace premarketing safety studies. In other words, is there a body of experience that might exist for an innovator, for a class of innovator drugs, that will allow for a limited premarket clinical program for a follow-on relying on, as the safety net, postmarketing surveillance.

It was, I think--it was stated, I don't know if generally agreed, that surveillance, per

se, and surveillance in the broad scheme, is not going to be informative of efficacy for most products. Postmarketing is, in many instances, the only means of detecting rare events. These are truisms for those of us, obviously, who work, in this area; that is to say, events not detectable in small premarket programs, but it is not, per se, adequate for assessment of causality by drug, particularly of common adverse events.

Not stated, but I think worth pointing out, spontaneous reporting, I think it is well understood, particularly in light of recent events, is not well suited to comparisons across products with regard to safety.

Some points that were actually raised that stimulated some discussion, again without answers, were around the detection of emerging safety issues with follow-ons, particularly, because that was the subject of discussion, in the postmarketing period.

I have two sub-bullets here that basically address the same overall concern. They were concerns about spontaneous reporting in a world of

multiple follow-ons because of an observed tendency of reporters not to list or name the brand of the product in a patient in whom--for the case of a drug-associated adverse event.

To the extent that there are potential differences from brand to brand--that is, after all, what we are trying to tease out--in order for postmarketing to have any utility with regard to inference of with regard to informing some of those emerging risks, the reporting of the specific product used is critical.

Again, on the same topic, there were concerns about switching for individual patients switched from one product to another similar product and the inability to determine the culprit agent in drug-caused adverse events. So, even if an event is known to be caused by a drug and, say, you are trying to determine whether the new product might be more prone to cause a known drug-related adverse event, the existence of multiple products and switching might lead to a lot of confusion in trying to identify the culprit agent.

The example given was that, for the erythropoietin experience and the pure red-cell aplasia problem, it was necessary, in order,

ultimately, to understand the genesis of the problem, to be able to identify the specific products that were involved.

There was some discussion of registries and I think it is safe to say that there was no one in the room, at least on the panel, who had any particular expertise in this area but, suffice it to say, it was stated that registries are often conceived and designed to address specific questions; that is to say, they are not another form of just sort of random monitoring of adverse events.

Some stated that if an innovator has a registry for a particular product then it would be axiomatic that the follow-on should as well. There was reassurance offered that many of the parties present had plenty of experience with registries and surveillance and that that wasn't a daunting prospect for anyone.

Then there was a question raised whether, given these uncertainties, particularly about follow-on protein products, should the safety of all new products, not just follow-ons but any new protein product, perhaps innovator or follow-on, as I said, should they be tracked in some way.

So, in summary, with regard to the "whens," when do you do studies, as I said, there are limits to the information from chemical characterization, PK/PD, although the parameters of these limits were not defined with regard to complexity and characterization.

The need for clinical studies and the type of clinical studies, obviously, should be tempered by knowledge of mechanisms of action and experience of some sort is seen as a guide to what constitutes a major change in manufacturing or, I guess, by extension, what would constitute potentially a difference between the process applied by an innovator and that by the follow-on manufacturer.

Which studies? The complexity of the product, the knowledge of its mechanism of action

dictates study requirements. Study standards and thresholds for clinical studies should mirror those for innovators after major changes and, with regard to postmarketing, I think the most important thing was the challenge of identifying culprit products for reported AEs.

I thank my fellow panelists and, for the audience who participated in the discussion, if there are any questions or comments, I am happy to hear them.

DR. CHEN: Thank you, Dr. Orloff. I, again, would like to thank all of you for your active participation in the very successful breakout sessions.

At this point, we will take a break. Since we are ahead of schedule, we will reconvene at ten past 10:00 if that is okay. It is a shorter break but this will probably let you out earlier.

[Break.]

DR. CHEN: We are ready to resume. The next session will be a summary of the workshop presented by various people from different

perspectives. The first one will be presented by Dr. Tony Lubiniecki who is Vice-President for Technology Transfer and Project Planning for Centocor. He will report from the Bio and PhRMA perspective.

Workshop Summary Bio/PhRMA Perspective

DR. LUBINIECKI: Thank you. I am Tony Lubiniecki, Vice President of Technology Transfer and Project Planning at Centocor, a Johnson & Johnson company. I represent the scientific working groups of both Bio and PhRMA who have attended this conference.

My purpose is to provide our perspective from the industry that has addressed unmet medical needs by providing safe and effective biopharmaceuticals to millions of people. We are proud of our achievements in improving the quality of life for our patients and take very seriously the role of our industry in the protection of the public health.

It is my goal to leave you with an understanding of how these proceedings relate to

what we, as an industry, have learned by developing, manufacturing and monitoring the use of about 100 approved or licensed biopharmaceuticals and about 400 investigational biopharmaceuticals in the past few decades.

The first area of discussion at this meeting was around analytical characterize of biopharmaceuticals. It is without doubt that the methods for biophysical, biochemical and biological characterization of biopharmaceuticals have greatly improved in the past several decades. I am sure they will continue to improve as scientific knowledge and tools continue to progress.

But there are several other things that we also feel are true. The confirmation of chemical structure is one of two enabling bases for the assumption about safety and efficacy for generic chemical drug products. If chemical equivalence and bioequivalence can be achieved for a chemical generic drug product, then one can typically assume that the safety and efficacy will be the same as well.

This truth works incredibly well for generic chemical drugs. But what is truth for chemical drugs is a largely untested assumption for

biopharmaceuticals. There is little data which support the concept that product characterization and bioequivalence alone are sufficient to enable safe and effective follow-on biopharmaceuticals.

In contrast, there are several scientific reservations about applying this generic chemical drug truth as an assumption to biopharmaceuticals.

This picture depicts at scale an, aspirin molecule, in red, and a molecule of erythropoietin, which is a medium-sized protein in green. Differences in size and complexity are obvious. Characterization methods are improving a lot but the level of understanding of the biopharmaceutical product molecules, especially concerning three-dimensional structure, does not begin to approach that that is possible for a small chemical molecule.

The substantially greater size is one barrier to characterization. Providing a chemical

level of assurance and greater molecular complexity is another factor. These factors combine to assure that all biopharmaceuticals are families of related molecules, in many cases, hundreds or thousands of different molecules and chemical structures rather than a unique identifiable chemical entity.

Characterizing the various constituents and their relative abundance remains an extreme challenge that is beyond many of the limits of the current analytical techniques.

The next slide shows that the erythropoietin molecule, with its three covalently linked carbohydrate moieties, which is docked in its dimeric receptor. Characterizing the chemical molecule is enough for a chemically based generic drug but it is not enough for a follow-on biopharmaceutical. Interactions of biopharmaceuticals with their targets often involve large amounts of molecular surface, of both the product molecule and its targets, often tens to a hundred times more surface area than for small chemical drugs.

Being unable, in many cases, to accurately map all of these interactions leaves undischarged a risk that a minor or unobserved molecular change in

a follow-on product leads to an unobserved interaction or a different interaction with the targets that leads to a different should or efficacy profile.

Mechanisms of action are often complex and incompletely understood. If the molecular interactions with the immediate target are known, there can be other differences downstream of the initial interaction. Some products, like interferons, are pleiotropic and activate multiple pathways in different ways.

In some cases, like tissue plasminogen activator, different product-related molecules interact with their plasminogen targets in subtly different ways. In many cases, biopharmaceuticals interact with multiple targets in the host with each interaction involving different parts of the molecule and impacting different clinical outcomes.

So, for example, one part of an antibody

may bind to a tumor cell. Another may trigger an immune response. And yet another may influence clearance from the blood stream. It is difficult to acquire a complete knowledge of these complicated interactions even after decades of product development and use.

These gaps in knowledge translate to a risk that a follow-on biological will be different from the innovator in some subtle way. This risk cannot be fully discharged by currently available methods of analysis.

Our sense of the presentations and discussions in the breakout groups at this meeting is that there is a growing scientific consensus that the chemical drug paradigm is not appropriate for follow-on pharmaceuticals.

The second truth about biopharmaceutical characterization which deserves a little bit of discussion is that the demonstration of similarity does not equal the demonstration of comparability. Several individuals affiliated with the generic industry have stated at this meeting and elsewhere

that follow up biopharmaceuticals can utilize comparability studies to establish the equivalence of a follow-on product to the innovator product just as innovator firms can do when evaluating the effects of process changes on the innovator product.

The generics industry argues that the same standards should apply to both situations and, once these standards are met, that they should then be able to use the safety and efficacy data of the innovator product and apply it to the follow-on biopharmaceutical.

The International Conference on Harmonization, or ICH, is an international effort among regulatory agencies in the three major regions of the world to harmonize the regulatory requirements used to regulate pharmaceutical products. In a recently approved guidance document called ICH Q5E on Comparability, comparable is described, and I quote, as "a conclusion that products have highly similar quality attributes before and after manufacturing process changes and

that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product has occurred. The conclusion can be based on an analysis of the product quality attributes. In some cases, non-clinical or clinical data might contribute to the conclusion."

This document also states, in Footnote 1 on the first page, that it is intended to apply to a manufacturer, in the singular, including any third party having a contractual arrangement on behalf of the market authorization holder or the developer for investigational product, again, all in the singular.

I was the rappateur for this document at ICH and it has been endorsed by both the FDA and by PhRMA. I can assure the audience that the specific intent of this document was to enable only comparisons within one product whether approved or licensed or investigational. The language of the document is very clear on this point and why is hopefully indicated in this table.

One manufacturer can look at any process

change and determine how it might have affected the quality attributes of the product as measured by the preponderance of evidence from the items which are shown in blue. So, when comparing product-from-process N plus 1 to product-from-process N, one can look at a variety of things that includes evidence from in-process testing, process validation results, drug substance, QC testing, drug-product QC testing, stability profiles, degradation profiles, characterization testing beyond QC and, if needed, nonclinical and clinical studies.

Some of these are depicted on this table in blue and the numbers in parenthesis refer to the product, of the number of samples times the number of tests which are typically done.

The manufacturer looks at all these results in light of the manufacturing history of the product, the CMC and clinical development history of the product, and then tailors the specifications for the product to this unique totality of data. The manufacturer can decide,

after reviewing all the evidence and all the history, whether comparability has been established by the evidence or not.

If comparability has been established, then the nonclinical and clinical data from the pre-changed product can be used with confidence to apply to the post-changed product. In contrast, a follow-on manufacturer or developer only has access to the drug product of the innovator. The follow-on manufacturer does not have access to the results of in-process testing, process validation, drug substance, CQ testing, API testing, stability profiles, degradation profiles, characterization testing beyond QC testing and also does not have access to the methods of the innovator or the test article or the standards.

Nor does the follow-on manufacturer have access to the innovator's clinical data that may indicate whether certain product variation influences clinical outcomes. Therefore, it is not physically possible for the follow-on manufacturer to establish comparability of the follow-on

biopharmaceutical to the innovator product.

All the that follow-on manufacturer can do is the evaluate the similarity of a follow-on drug product to the innovator drug product by different analytical methods from those used by the innovator. This is shown in the purple. Obligatorily, the follow-on manufacturer must use different specifications than the innovator since the follow-on manufacturer has a different producer cell line, different manufacturing process and different analytical methods.

What the follow-on manufacturer can establish by the study is that two products are similar but not that they are comparable. Therefore, follow-on manufacturers cannot use the non-clinical and clinical data of the innovator product and apply it to the follow-on product because the scientific basis of comparability, as defined by ICH Q5E, has not been established. Comparability simply does not apply to follow-on biopharmaceuticals.

A demonstration of similarity for

follow-on biopharmaceuticals aids the developer in the design of nonclinical and clinical studies. This paradigm is actually similar to the one in which the innovator finds himself when he attempts to develop second-generation products.

Biological characterization is important for all biopharmaceutical products, whether innovator or follow-on. Biological characterization is often a substitute for secondary, tertiary or quaternary structure of product-related substances which can be far more difficult to measure than primary structure.

Different levels of biological characterization are certainly possible. We have seen some descriptions of that here at this meeting. It can be done at the subcellular, the cellular, or at the intact organization level. But, because there is a less complete picture of the biopharmaceutical which emerges from physicochemical studies than typically happens with chemical drugs, the role of biological characterization for biopharmaceuticals is

substantially more important and this becomes especially true when the mechanism of action is incompletely understood.

To illustrate this concept in the 21st Century, we now understand the primary sequence of the entire human genome and have had this understanding for a few years. But yet the biological function of many vast tracks of genetic information is unknown. Thus, knowledge of chemical structure for complex substances does not equate to understanding of their biological function.

This statement is also true for the relationship between biopharmaceutical product structure and its biological function. Knowing the structure cannot typically predict biological function and the biological properties with certainty and completeness. Thus, biological characterization of a biopharmaceutical product is an essential feature for reducing risks to patients but it is not a substitute for nonclinical and clinical studies.

Despite these difficulties, developers need to use state-of-the-art analytical methodology to provide detailed biophysical, biochemical and

biological characterization of product-related molecules and impurities found in the product in order to reduce the risk to patients.

This concept should apply equally to innovator and follow-on biopharmaceuticals but no amount of follow-on product characterize can substitute for nonclinical and clinical data about product safety and effectiveness nor can it bridge to the clinical data of an innovator product. In these ways, biopharmaceuticals are fundamentally different from chemical drugs and the generic-drug paradigm cannot be applied to follow-on biopharmaceuticals.

Another area for discussion was nonclinical studies of pharmacology and toxicology. These studies should always be required of all investigational biopharmaceutical products because clinical studies will always be appropriate for biopharmaceutical products in order to manage the

residual risks resulting from complete lack of knowledge of structure and function and nonclinical data is needed to reduce any risk of taking investigation products of any sort into humans.

These nonclinical studies will also be needed to support the ultimate claims that will be made for the product in the marketing application. The existing body of nonclinical studies for current biopharmaceutical products and the safety record of the current biopharmaceutical products on the market makes a compelling case that the continued use of appropriate nonclinical studies in the best standard to minimize risk to patients not only in clinical trials using investigative pharmaceuticals but also to patients being treated with licensed and approved biopharmaceutical products.

Another area of discussion concerned pharmacokinetics and pharmacodynamics. As mentioned earlier, the bioequivalence is another key foundation besides chemical-structure equivalence for the generic chemical drug paradigm

which transfers the safety and efficacy data of the innovator product to the generic product.

While this works very well for generic chemical drugs, bioequivalence is not co-enabling for biopharmaceuticals for a variety of reasons. Sometimes, pharmacokinetics has little relationship to efficacy. Sometimes, pharmacodynamics cannot be measured or does not correlate with the measured levels of the biopharmaceutical. Sometimes drug levels measured are highly method-dependent and may not reflect the biological activity of the moiety responsible for the clinical efficacy.

Mechanisms of clearance and metabolism are frequently poorly defined for biopharmaceuticals and, even when pharmacokinetics and pharmacodynamics are measurable for biopharmaceuticals, their relationship to safety and efficacy must be known in order to interpret the results in a meaningful way.

Minor changes in the product that do not alter pharmacokinetics, pharmacodynamics, may significantly impact tissue distribution, receptor

interaction and immunogenicity and other key properties. We have seen a few examples of that discussed here at this meeting.

It is necessary to demonstrate bioequivalence for any follow-on biopharmaceutical where the claim of interchangeability with the innovator product is desired. However, bioequivalence, in itself, is not sufficient to support the generic chemical drug assumption of safety and efficacy for biopharmaceuticals.

The next area of discussion was around immunogenicity studies. Immunogenicity may arise from any of a number of possible causes including aggregates or other degradation products, the presence of adjuvants, the presence of process-related impurities and so forth. Some products are immunogenic inherently and that may be independent of any of the other causes that I have just listed.

The cause of immunogenicity may also be very different from product to product. Animal studies are not accurate predictors of product

immunogenicity in humans although these studies may indicate the potential role of antibodies to cause pathological findings as a result of antibody formation and binding to tissue antigens.

Immunogenicity of clinical significance has been observed in the development of a number of products including the interferons and thrombopoeitin and can result in clinical relapse while on treatment such as with the interferons.

In other cases, immunogenicity can lead to significant adverse safety outcomes. Management of potential immunogenicity issues for all biopharmaceuticals, investigational biopharmaceuticals, requires the availability of appropriate and sensitive assays for binding and neutralizing antibodies and for follow-up assays such as isotyping.

It is important to employ these tools to compare the level of immunogenicity of the investigational follow-on product to those of the appropriate innovator reference product and also to

look for clinical effects of the immune response on safety and efficacy. Such studies must be performed in each indication as the immune response to a number of biopharmaceuticals are well known to vary among the indication being treated.

The design of such studies should reflect the indication and the desired label claim. Some level of pharmacovigilence is appropriate of the follow-on biopharmaceutical as indicated by the recent experience of pure red-cell aplasia associated with one brand of erythropoietin after a postapproval formulation change was implemented.

Immunogenicity is too important a safety and potentially efficacy issue to be solely a post-approval concern.

The last area of discussion was around clinical safety and efficacy studies. No amount of product characterization can eliminate the need for clinical studies for a follow-on biopharmaceutical. No amount of clinical testing will remove all the risk that the follow-on product might perform in an inferior way.

More nonclinical testing will reduce this risk but not completely. The residual risk of follow-on product inferiority can be reduced by

appropriate clinical testing. The amount of clinical study needed for approval depends on the product, its intended use and the intended label claim. Postmarketing surveillance for safety issues, especially immunogenicity, must be adequate for the protection of the public health from unnecessary risks.

Postmarketing requirements should include the identification of all similar products used in all patients treated. This is especially of concern when an interchangeability claim is sought for the follow-on biopharmaceutical. Otherwise, pharmacovigilence studies could not discern what treatments were received by the patients who undergo adverse reactions.

In summary, I would like to leave you with seven thoughts. The first is that there is now overwhelming evidence that supports the view that the demonstration of chemical structural

equivalence and bioequivalence which supports the assumption of the same safety and efficacy with generic drugs. That this works really well for chemical generic drugs but there is little evidence that this chemical drug paradigm would work for biopharmaceuticals and some evidence that would not be able to be a supportable assumption for biopharmaceuticals.

Greater risks exist for follow-on biopharmaceuticals than chemical drugs that undetected differences from the innovator product are present and that these translate to risk in the assumptions about the equivalence of safety and efficacy.

As a second bullet, follow-on products cannot establish comparability to innovator products and, therefore, it cannot be assumed that follow-on products will have similar safety and efficacy profiles even if the characterization properties of the follow-on drug product are similar to those of the innovator drug product.

The third bullet is that the continued use

of appropriate nonclinical studies is the best standard to minimize risk to patients in clinical trials using investigational biopharmaceuticals and also for patients being treated with approved and licensed biopharmaceuticals. This applies to follow-on and innovator products equally. No amount of nonclinical testing will remove all of the risk from follow-on product and appropriate nonclinical testing will, however, reduce the risk but not completely.

Another important bullet is that appropriate assays should be used to compare the level of immunogenicity of investigational follow-on biopharmaceuticals to those of the appropriate innovator product and also to look for clinical effects of any immune response on safety and efficacy. Pharmacovigilence for immunogenicity issues is warranted post approval.

Another important point is the demonstration of human pharmacological bioequivalence is necessary to support any claim of interchangeability for a follow-on

biopharmaceutical. However, bioequivalence is not sufficient to support the generic chemical drug assumption of safety and efficacy for biopharmaceuticals.

Another point is that residual risk of follow-on products can be reduced by appropriate clinical testing. More clinical data removes more risk.

Finally, the amount and types of clinical information needed to reduce risk for follow-on biopharmaceuticals will depend on specific aspects of the similarity claim of the follow-on product and the use being sought, its product characterization and its indications.

We, of the innovator industry, are happy to have had the chance to participate in this workshop. It has been valuable to hear all the discussion and the points of view on this topic and even though comparability cannot be used for follow-on biopharmaceuticals, the discussion of all this information at the meeting here has, I think, shown a level of scientific consensus that an

integrated combination of all of the following elements, including product characterization, GMP controls and appropriate nonclinical and clinical studies can manage the risks associated with the development of follow-on biologicals.

This thought appears to be the consensus voiced here and it also seems to be the direction that the parallel debate and discussion in the European Union for biosimilars is heading as well.

I would urge the FDA to consider these scientific comments as its deliberates its way forward integrating with legal and public-policy considerations in a manner that will preserve the public health and protect patient safety.

Thank you.

DR. CHEN: Thank you, Tony. Next, I would like to welcome Mr. Gordon Johnston representing GPHA. Mr. Johnston is Vice President for Regulatory Affairs for GPHA.

Workshop Summary GPHA Perspective

MR. JOHNSTON: Thank you, Chi-Wan. Good morning everybody. I guess, to use the baseball

metaphor, we are kind of at the Seventh Inning stretch and coming down to the last inning here after a long and interesting workshop.

So I want to thank FDA and DIA for the opportunity to summarize the position of the Generic Pharmaceutical Association regarding the critical need to establish a definitive, flexible and scientific-based abbreviated approval process for affordable biopharmaceuticals.

This DIA and FDA Workshop has been a useful forum to confirm the science underlying biogenerics. We believe that this forum has, indeed, pushed us closer to the goal--that is, providing consumers with timely access to affordable biopharmaceuticals.

As numerous GPHA members noted during this forum, safety and efficacy are of the utmost importance and affordable medicine truly impacts the patient who might otherwise not have access. However, we always must be mindful of allowing science to be the engine that makes these important products available to those who are in need.

I think today it is not the question of if generic biopharmaceuticals will become a reality. It is really how. Recalling FDA's previous

experience with abbreviated data packages to approve biological products as well as the scientific principles outlined by Drs. Cooney, Sasisekharan and Kozlowski, among others, provided a firm foundation for us to move forward.

In fact, a lot has been written and said about the issue we will hear. The previous scientific debate that was held back in September, Congressional debates and in the media regulatory and other scientific arenas. But GPHA believes that all parties, including brands, academics and generics should agree on several important points.

First, all parties should agree that safety and efficacy must be the primary objective of establishing a definitive abbreviated process for approval of generic pharmaceuticals. It is an important and fundamental principle that will be ensured both by the industry and FDA.

Second, all parties should agree that

biopharmaceuticals comprise a continuum of complexity from relatively simply biopharmaceuticals such as penicillin that was mentioned by Dr. Cooney on Monday to those that are highly complex. As such, a one-size-fits-all paradigm for technical and regulatory approaches would be inadequate.

Third, while we should all agree, it appears that academic and the generic industry generally believe that an abbreviated regulatory process is clearly within the scope of current science. Thus, is it is possible to codify a regulatory process that would permit approval and marketing of a vast array of biopharmaceuticals with the relatively low to modest complexity and to expand that system in the coming years to permit approval of generic versions of even more complex products.

It is safe to say, however, that the parties do differ on some issues of the science. In general, the discussions have split along the lines of pure science and economic science. Given

the split of scientific and business interests, the parties will never agree on the fundamental question of this forum which is, can a definitive, flexible, abbreviated approval process be immediately established that will enable the timely introduction of safe and effective affordable biopharmaceuticals.

Our industry responds to that with a resounding yes. Yes; we do believe it is time to codify a regulatory pathway for the introduction of biopharmaceuticals and for FDA to issue its recommended scientific principles on this abbreviated pathway.

These principles should be based on the agency's historic experience with these products as well as the scientific approaches discussed at both workshops on this topic. When one filters the rhetoric, it is abundantly clear that science does support such a framework. Science and technology have progressed rapidly. Just a decade ago, we would not be discussing the possibility of affordable biopharmaceuticals.

As Acting Commissioner Crawford said last year, "Two years ago, the scripted answer was, they are too complex. We can't do that. And everybody

knows that you can't have generic biologics. Well, they are not any less complex but the means of evaluating them biochemically and with instrumentation is very much improved over the past two years. We are very committed to try to put in place a reasonable way of dealing with generic biologics. No longer will we answer by saying, the complexity is too great, we will get back to you in another decade. Those days are over and we have to put a system in place to deal with it."

In fact, Dr. Cooney, the Acting Chair of FDA's CDER Advisory Committee for Pharmaceutical Science, remarked that, "It is the incorporation of prior knowledge, innovation of new technology and new methods and publicly available data that defines the operative space we work in. Approval of generic versions of biopharmaceuticals can operate within those parameters by using current knowledge coupled with modern techniques and

methods that are more predictable and less costly."

The immediate implementation of a definitive abbreviated framework driven and supported by science must be based on the principles of the comparability. It is not new. Rather, it is an extension of the scientific principles on comparability and abbreviated approval processes that was formalized in the FDA almost a decade ago. These very principles already have been used to permit brand manufacturers to make changes in production process, cell line, manufacturing site, formulations among others. This has been done for recombinant proteins, monoclonal antibodies and, at times, without clinical data supporting the safety and efficacy of those changes.

FDA has also permitted albumins, allergenics, among other products, to come to market with abbreviated data packages.

The primary basis for the abbreviated approval process should be the comparison of the brand and generic biopharmaceutical. A scientific

framework for the approval of abbreviated data packages, should be based on the complexity of the product on a case-by-case basis.

At the heart of this approval system are product comparative characterization studies and, as we all recognize, the state of the art of characterization technology consists of physical, chemical, immunochemical and in vitro biological studies. These physical and chemical studies include, but are not limited to, proteins, sequences, disulfide linkages, 3-dimensional structures among others.

Studies also use analytical tools such as mass spec, circular dichroism, near IR, NMR, among others. Significantly, these tools have been refined to provide dramatic increases in sensitivity over time. For example, at this meeting, we heard that mass spec methods have increased in sensitivity by about 1 million-fold over a ten-year period.

Moreover, it is time to recognize that FDA has accepted comparative characterization studies

under a comparability approach as evidence to support many brand product and manufacturing changes. In fact, FDA's Dr. Kozlowski opined that, under the agency's comparability approach, structures equal function if comparability can be assured.

In other words, based on adequate characterization and historical use, the biopharmaceutical product can be recognized as safe and effective for its intended use based on analytical and biological characterization.

And, as we have heard from MIT professor, Dr. Ram Sasisekharan, not only has the technology to characterize proteins significantly progressed but, also, the science and methods to characterize glycans. Current technology allows us to characterize simple to moderately complex glycan products and, as far as the more complex products, he noted that technology exists to build an equivalence window using a suite of commonly available analytical tools to establish product aspects that can define equivalence. It is

possible to do this today and we support this concept.

Thus, many analytical tools are readily available to compare physical, chemical and biological parameters of affordable biopharmaceuticals and their brand-name counterpart and we believe that scientifically sound selection of orthoganal parameters in the state-of-the-art methods, ones that match the complexity of the product, can result in a complete picture of most biopharmaceutical products.

Of course, the extent of other studies at subsequent levels should be determined on a case-by-case basis. This can be accomplished according to the level of understanding gained from the initial physical, chemical and biological analyses. The range of studies would include PK studies, PD studies, animal studies and targeted clinical studies using surrogate markers or phase III clinical endpoints, if necessary.

We strongly believe that human PK and PD studies, in conjunction with adequate

characterization, can support approval of many affordable biopharmaceuticals and, in some of the very complex cases, additional clinical studies may be needed to confirm safety and efficacy of the product.

Rest assured, the generic biopharmaceuticals will follow the same rigorous pharmacovigilence requirements as their brand-name counterparts.

Dr. Mark McClellan, the former FDA Commissioner, supports these concepts. Last year, he said, "The science may be adequate now to proceed on several relatively simple biologics that were approved as NDAs. This includes certain older forms of HGH, insulin and some interferons. These initial steps will also provide a useful foundation for considering the further scientific and legal development required for supporting large-scale generic biologics in the years ahead." We agree with his concept.

Finally, given that this is a question of science, Congress should ensure that those

decisions are made in the arena best suited for resolution; namely, within FDA. American consumers rely on FDA to make the rights scientific decisions regarding brand-product formulation, manufacturing and specification changes based on comparability and risk assessment.

The FDA approval process remains the world's gold standard for drug approvals because it is based on robust application of science and technology. As a result, American medicines are, and continue to be, the safest in the world.

We need to avail ourselves to the FDA' scientific expertise and judgement. FDA often makes risk-based decisions regarding ground-breaking therapies with data from limited testing and patient exposure. Examples are orphan drugs and other accelerated-approval mechanisms. FDA should apply the same risk-based decision making to all facets of the approval process for biopharmaceuticals including immunogenicity. If the risk profile is the same or less, FDA should be able to approve the product and provide consumers

with a choice.

Again, going back to Dr. McClellan, he remarked that, "Without a system to allow approval of lower-cost alternatives, spending on biomedical innovations would become unsustainable." We couldn't agree more. Already marketed biopharmaceutical products account for approximately $30 billion in the U.S. and represent about 12 percent of the total sales and that is expected to rise to about $60 billion by 2010.

Because of these high costs, biopharmaceuticals will consume a greater percentage of healthcare expenditures in the future and substantially burden the healthcare purchasers including government, employers and consumers.

Just to put this in perspective, an average cost to a major U.S. employer for a one-day supply of a biopharmaceutical drug is about $45 while the traditional small-molecule product is about $1.66 per day. Today, generic medicines can cost up to 80 percent less than their brand-name counterparts and can save millions each year.

Affordable biopharmaceuticals, even if they represent only a modest segment of the market, would create billions of dollars in savings in the healthcare arena.

For these versions of generic biopharmaceuticals to reach the market, FDA must take an affirmative action now to create a definitive, flexible and abbreviated approval pathway. Four years ago, FDA announced it would be working on two biological guidance documents on insulin and growth hormone. According to news reports at that time, those guidances were expected to be issued within 60 days. More than 1,000 days later, we are still waiting.

Based on the existence of sound science, we strongly urge FDA to immediately issue its white paper as the agency guidance documents to provide timely advice to the industry. Given the significant lapse of time since FDA's initial announcement, it is only right for FDA to provide an accelerated time line so that the agency can demonstrate to the public that progress is being

made on this front.

We also urge FDA not to hold up approval of products while it prepares and issues these guidances. In addition, Congress should immediately provide FDA with the authority to make scientific decisions so that there would be no gaming of the approval system by special interests and allow FDA to do what it does best, evaluate science and approve drugs.

In sum, the nation debates how best to provide financial security for aging Americans. We can't neglect the available strategies to ensure that prescription medicines and good healthcare remain affordable.

The good news it that science and biopharmaceutical technology is now producing exciting new medicines that provide enormous benefit to patients each year. The bad news is, without generic versions, the cost of these medicines will indefinitely place a tremendous financial burden on the healthcare system. Fortunately, Congress, with the assistance of FDA,

can help secure the future of American health again by establishing a definitive abbreviated approval process for biopharmaceuticals.

There is no reason to delay the consumer access to biopharmaceuticals when the sound science supports their approval under a shortened approval pathway. This workshop demonstrated there are scientific approaches that permit abbreviated data packages that will assure safety and efficacy of low- to moderately-complex biopharmaceuticals.

We look forward to a continued partnership with to finalize the abbreviated pathway and to resolve the outstanding issues surround the more complex biopharmaceutical products.

Thanks for the opportunity to be here today.

DR. CHEN: Thank you, Gordon.

Next, I would like to ask Dr. Keith Webber to come up here to give a summary from our perspective.

Workshop Summary

DR. WEBBER: We just went through the

seventh-inning stretch. I guess it is eighth inning. I will be relatively brief. First off, though, I did want to thank everyone who really made this meeting possible and that is the folks who worked on the breakout sessions, worked on the plenary sessions. Of course, with the breakout sessions and the plenary sessions, they would have been relatively pointless if we hadn't had the audience here to participate in the discussion.

I think everybody really did--as I said, at the beginning of this meeting, that this was going to be a working meeting. I think everybody really did work hard and provided us with a great deal of information that will be valuable as we move forward in drafting guidance documents in this area.

Just a few things in closing. Presentations from the meeting are going to be available on the DIA website. The presentations from the breakout sessions will also be available, and the summaries from those, on the FDA website. A link for the presentations is going to be sent to

all registered attendees by DIA. Transcripts are going to be available to all attendees from DIA as well.

If there is additional information, I just want to reiterate that we have opened the docket--that is No. 2004N0355 for a 30-day period. It is not open indefinitely. We just wanted to open it for an additional time surrounding this meeting. It will close on March 16. Really, we just want to make sure that we get as much information from all interested parties as possible submitted to the docket so that we can utilize that information.

Now, it is going to be difficult to summarizes the summaries of the summaries. Everyone did a great job of summarizing the breakout sessions already so I am not really going to go through all those.

These little guys here are sort of my introduction to concepts that we have dealt with here and why I have them up there is, although it may be relevant to talk about them as being

potential patients of your products, and maybe actual patients of your products, the reason that they are up there is because cognitive development in this pre-school age range, one of the cornerstones of key concepts they deal with is what is same and different.

That is what we are dealing with now, those of us who are quite bit older than that, still trying to figure out what is same and different and what factors must be considered when you are determining if things are same or different and, if they are different, what are the impacts on you as a user of those items.

Another concept is the idea of risk and benefit. Potential benefits associated with the marketing follow-on-protein products. Potentially, there is decreased cost to patients. There could be increased availability of drugs. There have been some comments here throughout the meeting of potential increased quality of drugs and that has been brought up as being potentially because the follow-on manufacturers have a limited or a smaller

target to shoot at in some ways based upon developing their specifications from material which is on the market which may end up providing them with narrower ranges.

Also, I think, from the competitive perspective, it does have the potential to drive increased quality of manufacturing with innovators as well.

What are the potential risks? Well, we have heard about potential lower efficacy for these products. That is a risk that has to be dealt with. There could be more or different adverse events associated with these products. Another risk that we have heard about and is potential is a decreased free exchange of information within the area of biotechnology product development.

These are all the risks and things that we have to deal with as we move forward.

Now, consensus; where are we? I think, summarizing, a lot of people laughed when they thought we were going to get some consensus out of this meeting, but I really had hope and I think

that, in many regards, the hope has been met. So here is a list, in the next few slides, where I think we have reached consensus.

One is that some biotech products are more complex than others. Also, that clinical safety and efficacy cannot be established from product characteristics alone. Somebody has got to do clinical trials to demonstrate safety and efficacy. That may be the innovator. That may be, in some cases, the follow-on producer as well depending upon the risks associated with that.

If I could just step back a little bit to make one point about that, really to make it clear that you can't determine safety and efficacy by looking at the product all by itself. So, de novo, you need to have some clinical safety and efficacy data. Protein pharmaceuticals are potentially, and many, if not most cases, immunogenic.

Now, complexity; how do we deal with complexity. I think there is general consensus and agreement that it is a multifactorial parameter for products. You have intrinsic product complexity

which is, essentially the product--any individual molecule of the product has its complexity. This is associated with its size, its shape, whether it is a multi-subunit product or not, what sort of post-translational modifications it has.

Now, within the population of molecules, there is heterogeneity. Some have essentially all these other intrinsic properties of their own so they may be slightly different sizes, different shapes. Some have different post-translational modifications.

Then, of course, there are differences in impurities and contaminants that we have to deal with. There is also functional complexity of the products. Some products act as antagonists. They may just simply bind to a site and block the effector from binding there. They may be an agonist in that they have to bind and also they have to elicit some activity in vivo that is associated with the endogenous product or component that they are mimicking.

Some of them have enzymatic activities

that have to be active in order for them to be functional. Some of them not only bind but they have effector function as well which is similar along the lines of an agonist but can be considerably more complex because they may need to recruit other aspects of the biological system in which they are acting.

There is complexity associated with the recipients of the drugs. Some indications are more complex than others. The patient population; some folks are healthy. Some people are ill. Some people are terminally ill. Those are factors that need to be taken into account when assessing the complexity of any given product. What concomitant medications are people taking and how does that impact on the risks associated with the product that they are receiving.

Some products have multiple indications so we have to think about that as well. Are there cases where each indication is unique enough or some indications are so unique that we would require specific clinical data for one and not for

another, clinical trials for one and not for another.

Science; I think we all have heard science a lot in the summaries today and I think that is a very central point of consensus I think that we have here, that science has got to drive, whether you are an originator company or if you are a follow-on company. It has got to drive product development. It has got to drive your product characterization. It has got to drive your manufacturing process, the develop of it and its continued appropriateness and do what you want it to do to producing a quality product.

It has got to drive the need for clinical data and how much clinical data is necessary for any particular indication. It has got to drive the FDA reviews as we receive applications and it has to drive our approval decisions, either to approve or not to approve.

We have, I think, consensus on quality of products and that is that all pharmaceutical products, whether manufactured--no matter who they

are manufactured by--those manufacturers have to strive to produce the highest quality products. I think that is a perspective that I have heard from both sides throughout this meeting and I think it is important to ensuring that the American public has the products of the highest quality.

I believe that might be my last slide.

One other item that I was asked to--that just came up was regarding audio for this last close-out day. There is an audio, audiocasting, I guess you would call it, that is available and will be available for the rest of the week. You get audio by calling 866-383-3135. This is available for one week and it will end on the 25th of February at 5:00 p.m. So if you have additional folks who would like to hear that or if you would like to re-hear some of the closing statements from this meeting, it is available there.

So I know everybody is in a big hurry to get out of here, probably, because it has been a long a very--a lot of hard work this week. So, at this point, I would like to invite Dr. Azaj Hussain

up to give the final closing remarks for this meeting.

Thank you.

Closing Remarks

DR. HUSSAIN: Good morning. I have spent much of this workshop sitting back and listening and also sort of formulating the closing remarks which also sought input from Dr. Woodcock and many others in this room.

The key challenge, I think, for the closing remarks is to, in some way, summarize some gaps that might exist in how we manage the process going from this workshop. So that is the basis of my talk and the closing remarks

I think the workshop goals and objectives that we set before we came to this workshop were quite challenging. The summaries that you heard this morning provided a fair advancement in our thinking in how we deal with the terminology and describing the type of data needed to ensure safety and efficacy. So I think we made more progress than actually, personally, I had anticipated.

But, at the same time, I think we have to step back and really ask the question, to what extent did we accomplish the set goals and

objectives, what gaps continue to exist, why, and how can these gaps be filled. At the same time, I think, listening to the different points of view, we still have a need to take time out in some ways to reflect, as a community, not as one association or the other association, because I think we all share a set of common values of serving our patients.

I think we need to take some time out to reflect, as a community, and keeping the needs of the patients paramount in our reflections. I think some of the challenges that remain in filling this gap--this is what I would like to propose to you as points to consider--as part of your reflection, I think, if you would consider the challenge that we have, the challenge essentially for this meeting was the scientific basis for sound decisions related to follow-on protein pharmaceuticals, reflect back what should be the goals and

characteristics of such decisions be, how do we ensure decisions as sound, acceptable, not just by us but by the public also, transparent and also facilitate continuous learning and continuous improvement throughout the industry not just in one part of the industry.

I think there are several components of the challenge which I would like to sort of emphasize. We may not have addressed them adequately at this workshop. Risk-based scientific decisions on pharmaceutical quality, I think, has been the focus of much discussion but I feel that the work "risk" has been used quite liberally without paying attention to what that word really means.

Risk is a combination of the probability of the occurrence of harm and the severity of that harm. So I think it is a combination of the two. It is not just harm, itself.

Uncertainty has been used many times, uncertainty with respect to severity of harm and of probability of its occurrence, I think, is the

challenge that we face in making decisions. But, also, uncertainty with respect to modulating factors. What are the critical quality attributes that relate the probability of harm as well as the severity of harm, I think, is a challenge.

One aspect which we have not discussed at length is the variability component; how does variability contribute to the probability of the occurrence of harm as well as the severity of that harm. In risk-based decisions, I think, in reality, and to be pragmatic, all decisions have to be taken under uncertainty and variability. Often, we sort of mix things together. Uncertainty and variability are, generally, lumped together but there is an advantage of separating that out.

Epistomoligic uncertainty or lack of knowledge points to the question, how do you know what you know. That is the fundamental question that we need to ask. There is an advantage to make a distinction between uncertainty and random variation. In fact, this was a proposal to the President by the National Research Council in how

we should develop policy. This was published in 1994, Science and Risk Assessment.

Uncertainty forces decision-makers to judge how probable it is that risk will be overestimated or underestimated for every member of the exposed population, to that, from an analytical sense, goes to the accuracy of your decision whereas variability forces them to cope with the certainty that different individuals will be subject to risk both above and below any reference point one chooses. So variability goes to the imprecision aspect of the decision.

Now, the challenge we face is we have a wonderful means of making risk-benefit decisions as we approve a drug product. But, at the same time, what I would propose if, if you would accept, just as a hypothetical one, approval decision at FDA defines an acceptable risk:benefit ratio of a proposed product.

On the one hand, you have no behavior. On the other hand, you have harm. So the label that we approve essentially provides information to

allow physicians and patients to use the product effectively to be within that acceptable risk:to:benefit ratio. There are many, many factors that contribute to that in addition to quality.

But, how do we develop our clinical-trial product to achieve that label condition because the clinical trials are based on that clinical-trial product that we used.

Following approval, you have many production lots and you have to maintain quality, and that quality attribute of your product has to be linked back to clinical trial, the label, and has to be useful for the patient population.

The challenge we face is we often confound uncertainty, variability and risk into one thing. The way we approach product and process development, the multifactorial aspect, I think, we have no choice but to do some of this. Approval decisions are clearly the risk:benefit ratio assessment. Often, intrinsic safety and efficacy of a new molecular entity are confounded with its

product and manufacturing process. That is the most efficient way of doing development.

You have multifactorial aspects of pharmaceutical products and manufacturing processes and they have increasing complexity as time goes by. Establishing constraints based on prior knowledge and limited development experiments are the pragmatic approach to developing specifications and controls and so forth.

We often rely on procrustean standards and specifications to cover worst-case scenarios by limitations of time, materials and so forth. Now, procrustean standards simply means you are 80 to 125 would be adequate to cover everything. That is the word that I learned from Professor Bennett at our advisory committee. Procrustean goes back to Procrustes where the lord of whoever this person thought there should be only one size for the bed. So, if your legs are too long, you chop off your legs.

So that is how we often approach standard settings and specification which often means

managing--which is often necessary for managing decision efficiency. But that includes lost opportunity and an assumed risk minimization. Now, the challenge I think we face as we move forward from this workshop is uncertainty management. It is the first step towards risk-based decision. We often force the equality; uncertainty equals risk. But there, also, we mean harm, not the combination of probability of occurrence of harm and severity of harm.

Uncertainty can include opportunity, perceived risk and risk, opportunity to improve opportunity to reduce cost, opportunity to do lots of thing that we often sacrifice on the basis of a presumed risk of because the risk is unknown.

Uncertainty has to be managed to realize opportunities, minimize risk and also the factor that we did not discuss extensively at this workshop is to define acceptable variability or comparability or however you want to put this. This is a great challenge. Generally, uncertainty increases with increasing complexity. Increasing

information knowledge can decrease uncertainty, but not always.

Increased knowledge can increase uncertainty, in some cases, possibly destabilizing existing consensus. A wonderful example is you have more modern analytical methods, and so forth, so when you go back and look at it, so that is an example where uncertainty can increase and you have the possibility of destabilizing existing consensus.

Anomalies will always exist and often will be exploited by one part of the segment of the industry or the other. So those are the challenges that we have to manage. But, also, uncertainty management includes establishing consensus which was one of the goals of this workshop. But consensus doesn't mean unanimous.

Consensus is a moving target. You have conceptual revisions recur in science. You have diversity of scientific methods and multiple interpretation. That is one of the significant challenges we face. Scientific proof and

persuasion has a social dimension which we did not cover in this workshop.

So what is scientific consensus and what are the steps to getting to that. The first step, obviously, is scientific debate by scientists. Such debate are helped by increasing knowledge and we heard some of that in this discussion, does FDA have the prior knowledge, can we bring some of this to bear. So that clearly can help. But increasing science or increasing the knowledge base often is not a means to get scientific consensus when you think about how we have to deal with the broader social consequences.

But, at the same time, I think, based on this discussion, much of what we learned from this workshop, are we moving towards a general scientific decision framework, one size doesn't fit all, but if we have a general scientific-decision framework that may be different for different--the details will be different for different products and so forth. That seems to be a direction.

But, also, we have to seek and ensure

public acceptability of a proposed scientific-decision framework. Somehow, the FDA process of openness, our draft guidance for comments and other aspects like advisory-committee discussions and so forth is a means to achieving that.

One previous discussion which may be relevant to this workshop is a critical-path initiative that we proposed and discussed at our advisory committee. This occurred on the 19th of October, 2004, so if you want details of this proposal, it is available on our website.

The goal here was to develop a common scientific-decision framework for addressing uncertainty in the context of complexity of products and manufacturing processes in our Office of New Drug Chemistry, Biotechnology Products and Generic Drugs. This is an OPS proposal since the Office of Pharmaceutical Science manages these offices.

We were seeking to find a common decision framework to manage the decisions in these three

offices. The motivation was, or is, a common decision framework irrespective of the regulatory part, a process for these products will provide a basis for efficient and effective policy development and regulatory assessment to ensure timely availability of these products regulated in these offices.

So, irrespective of what the regulatory part of it is, the science should be common and the decision framework should be common and you address the differences through understanding and defining and categorizing complexity and actually defining and categorizing uncertainty that we have in our decision-making process.

So, something to consider.

Another point to consider, as you leave this what I think is a great conference is, in the context of post-approval changes, generic drugs and the concept of follow-on-protein products, the primary goal of a scientific-decision framework should be to ensure that an approved product is expected to have the same clinical effect and

safety profile when administered to patients under the conditions specified in the labeling. So that is the primary goal of what we are trying to achieve.

Furthermore, the other goals include identifying and elimination or minimization of unnecessary human and animal testing as part of the goals for this decision framework.

Now, those are the goals. Some of the characteristics of our decision framework, points to consider; reducing uncertainty to make risk-based decisions and to define acceptable variability. That is the aspect I think we would need to cover further as we discuss. The challenge is this; you cannot actually make a risk-based decision in an uncertain scenario. Uncertainty precludes risk-based decisions if you define risk as I defined it, as the probability of occurrence of harm as well as the severity of that harm.

The characteristics of whatever decision framework we develop should facilitate innovation, continuous improvement and efficiency throughout

the industry, through the agency, but not just in one part of the sector and so forth.

But, equally important, is we have to take a systems approach to facilitate a proactive decision over a life cycle of a product. Now, some significant discussion occurred following approval; adverse-event reports, how do yo manage that. But, also, keep in mind that we have difficulties with manufacturing. You will have auto-specification results. You will have deviations. You will have all of those. And how would we also include that in our decision framework is an important consideration.

So, with that, let me summarize. I think FDA will take into considerations information, ideas and perspective discussed at this workshop. We plan to issue a background document and draft guidances for public comment. Dr. Woodcock summarized that and we have a background document that traces the history, some of the aspects, that we hope to issue plus draft guidances.

We will continue to collect information,

as Keith pointed out. But, at the same time, I will request a humble request to all of you is we would take time out to reflect, as a community, not as one part of the segment or the other, keeping the needs of the patients paramount in our reflection.

I thank you for participating and contributing your ideas, and have a safe trip.

Thank you.

DR. CHEN: As the workshop is coming to a close, I, again, would like to thank you for your participation. I would to also thank the members on the Planning Committee, the speakers and the moderators for their hard work in making this workshop a success and, most of all, your participation.

I hope you have found this workshop to be useful in that it is an opportunity for you to express your professional experience, your scientific opinion and share your opinion and experience with the rest of us.

Thank you. FDA certainly will take all of

your input into consideration as we move forward to establish our policy and guidance on these important issues.

Thank you. Have a safe trip home.

[Whereupon, at 11:20 a.m., the meeting was adjourned.]

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